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Risk factors for Kaposi's sarcoma among HHV-8 seropositive homosexual men with AIDS

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Kaposi's sarcoma (KS) is a frequent complication of the acquired immunodeficiency syndrome (AIDS) in homosexual men. Risk factors for developing this malignancy are uncertain, other than immunosuppression and coinfection with human herpesvirus 8 (HHV-8). We therefore examined factors associated with KS in a cross-sectional analysis of 99 cases among 503 HHV-8 seropositive homosexual men with AIDS. Data were collected by computer-assisted personal interviews and medical chart reviews. HHV-8 seroreactivity was determined by enzyme-linked immunosorbent assay for antibodies against HHV-8 K8.1 glycoprotein. KS was significantly less common in blacks compared to whites [risk ratio (RR) = 0.4; 95% CI = 0.2=0.8] and more common in subjects who had completed college (RR = 1.7; 95% CI = 1.1–2.7) or had annual income greater than $30,000 (RR = 1.5; 95% CI = 1.1–2.2). KS was less common in cigarette smokers (RR = 0.6; 95% CI = 0.5–0.9) and users of crack cocaine (RR = 0.4; 95% CI = 0.1–0.8). KS was less common in bisexual men compared to men who were exclusively homosexual (estimated RR = 0.6; 95% CI = 0.4–0.9) and inversely associated with number of female partners. KS was also less common in men who had received pay for sex (RR = 0.6; 95% CI = 0.4–1.0). These cross-sectional associations could be biased by potential differences in relative timing of HHV-8 and HIV infection, a postulated determinant of KS risk. Alternatively, our findings may reflect factors protective against KS in individuals infected with HHV-8. Future research should focus on identifying practical measures for countering KS that do not increase the risk of other diseases.
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Key words: Kaposi's sarcoma; human herpesvirus; AIDS-related malignancy

Human immunodeficiency virus (HIV)-related Kaposi's sarcoma (KS) is an opportunistic neoplasm caused by coinfection with human herpesvirus 8 (HHV-8).[1–3] Previous studies of acquired immunodeficiency syndrome (AIDS) patients have identified risk factors for infection with HHV-8, including sexual activity among homosexual men, intravenous drug use and blood transfusion.[4–9] However, only a few studies have investigated risk factors for progression to KS among individuals coinfected with HIV and HHV-8.

Homosexual men may be at greater risk of AIDS-related KS than are members of other HIV transmission groups, even adjusted for differences in prevalence of HHV-8.[1] Furthermore, HHV-8-infected individuals progress to KS at different rates or frequently not at all,[10–12] suggesting the existence of cofactors that influence risk. We therefore examined potential associations with KS in a cross-sectional analysis of HHV-8 seropositive homosexual men with AIDS enrolled in the AIDS Cancer Cohort Study.

Material and methods

The National Cancer Institute's AIDS Cancer Cohort Study is directed toward identifying rates and risk factors for HIV-associated malignancies. From October 1997 to January 2000, 2,803 persons with Centers for Disease Control and Prevention-defined AIDS[13] were enrolled from 24 AIDS treatment centers located throughout the United States. In the current analysis, 36 study participants were excluded because their medical histories were not available for review. Of the 2,767 remaining subjects, 620 (22%) had antibodies to HHV-8 at enrollment; 503 (81%) of the seropositive subjects were men who reported having had homosexual sexual contact at least once in their lifetime. Since 99 (96%) of the subjects with KS prior to enrollment were homosexual men, analysis of KS risk was restricted to this group. All subjects gave written informed consent, and institutional review boards at the National Cancer Institute and at collaborating institutions approved this study.

Information on demographics, occupational history, medical history, lifetime use of tobacco and nitrate inhalants, use of alcohol and other recreational drugs in the previous 12 months, as well as lifetime sexual behaviors, was collected in person by trained interviewers using a computer-based questionnaire. Prior diagnoses of AIDS-defining conditions were obtained by review of medical records.

Plasma samples were tested for evidence of HHV-8 infection using an in-house enzyme-linked immunosorbent assay for antibodies against K8.1, an HHV-8 structural glycoprotein, as previously described.[14,15] A positive reaction was defined as an optical density more than 0.75 units greater than the average reading of 3 negative controls on the same plate.

Univariate associations with prior or current KS were assessed by risk ratios (RRs) and 95% confidence intervals (CIs). Dose-response trends were examined by chi-square tests, with $p < 0.05$ considered statistically significant. To account for potential socioeconomic differences between races, analyses of the effects of income and education were conducted separately for blacks and whites. Variables with a statistically significant ($p < 0.05$) univariate association with KS were evaluated in multivariable logistic regression models to adjust for potential confounding.[16] To avoid overestimating associations with a common condition, modeled odds ratios and 95% CIs were corrected for comparability to risk ratios.[17]

Results

Twenty percent of the HHV-8 seropositive homosexual men in the AIDS Cancer Cohort had KS at enrollment. The prevalence of prior or current KS did not substantially vary by age (Table I). KS prevalence in blacks was less than half (RR = 0.4; 95% CI = 0.2–0.8) that in whites. Compared to lower-income men, subjects with

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TABLE I – DEMOGRAPHIC VARIABLES AND UNIVARIATE ASSOCIATIONS WITH KS

Characteristic[1]	*n*	KS (%)	RR (95% CI)
Age			
< 40 years	218	42 (19)	
≥ 40 years	285	57 (20)	1.0 (0.7–1.5)
Race/ethnicity			
White	326	75 (23)	
Black	121	12 (10)	0.4 (0.2–0.8)
Hispanic	45	8 (18)	0.8 (0.4–1.5)
Income			
< $15,000 per year	252	45 (18)	
$15,000–$30,000 per year	115	18 (16)	0.9 (0.5–1.4)
$30,000–$60,000 per year	71	18 (25)	1.4 (0.9–2.3)
>$60,000 per year	63	17 (27)	1.5 (0.9–2.5)
Whites			
< $30,000 per year	215	46 (21)	
≥ $30,000 per year	109	28 (26)	1.2 (0.8–1.8)
Blacks			
< $30,000 per year	109	9 (8)	
≥ $30,000 per year	12	3 (25)	3.0 (0.9–9.7)
Education			
Less than college graduate	188	24 (13)	
College graduate	250	55 (22)	1.7 (1.1–2.7)
Whites			
Less than college graduate	101	16 (16)	
College graduate	178	43 (24)	1.5 (0.9–2.6)
Blacks			
Less than college graduate	66	5 (8)	
College graduate	41	5 (12)	1.6 (0.5–5.2)

[1]Numbers do not sum to total of study participants because of other or missing responses.

annual income greater than $30,000 had an increased prevalence of KS (RR = 1.5; 95% CI = 1.1–2.2), with the effect of income more pronounced among blacks than among whites (Table I). College graduates were almost twice (RR = 1.7; 95% CI = 1.1–2.7) as likely to have had KS as those who did not graduate from college, and the association did not vary by race.

Of the 503 men in the study, 331 (66%) reported lifetime consumption of more than 100 cigarettes. Smoking was associated with a significantly lower prevalence of KS, with only 17% of current or previous smokers having had a prior diagnosis of KS (RR = 0.6; 95% CI = 0.5–0.9; Table II). The association was slightly stronger in ever smokers of one or more packs per day (RR = 0.6; 95% CI = 0.4–0.9) than in those smoking less (RR = 0.7; 95% CI = 0.5–1.1) and in those who had smoked more than 20 years (RR = 0.6; 95% CI = 0.4–0.9) than in those who had smoked fewer (RR = 0.7; 95% CI = 0.5–1.1), but neither trend was significant.

Use of crack cocaine in the 12 months prior to enrollment was associated with significantly lower prevalence of KS (RR = 0.3; 95% CI = 0.1–0.8), but use of cocaine in other forms such as powder was unrelated to KS (RR = 1.2; 95% CI = 0.8–2.0). In a model that included both of these exposures, the inverse association with crack cocaine use persisted (RR = 0.5; 95% CI = 0.1–0.8), and the relative risk associated with other cocaine use was materially unchanged (RR = 1.2; 95% CI = 0.8–1.7). KS prevalence was also somewhat lower with heroin (RR = 0.6) or amphetamine use (RR = 0.5), and somewhat higher with alcohol, sedatives, or frequent nitrate inhalant use, but none of these associations was statistically significant.

Men who had ever had sexual intercourse with women were only half as likely to have KS (RR = 0.6; 95% CI = 0.4–0.9; Table III). Various heterosexual activities were inversely associated with KS. The risk ratios for KS associated with having more *vs.* less than 5 female partners for vaginal intercourse, fellatio, or cunnilingus were 0.5 (95% CI = 0.3–0.9), 0.5 (95% CI = 0.2–0.9) and 0.6 (95% CI = 0.3–1.2), respectively. Furthermore, increasing number of reported female sexual partners was associated with decreasing likelihood of KS. Compared to having no female partners for vaginal intercourse, the risk ratios were 0.7 (95% CI = 0.5–1.0) for 1–5 partners and 0.4 (95% CI = 0.2–0.8) for > 5 partners ($p_{trend} = 0.002$). In general, sexual activities with males had an opposite association. Men whose lifetime sexual history included receptive anal intercourse or fellatio (receptive or insertive) with more than 20 male partners had a modest (but statistically nonsignificant) increase in KS prevalence (Table III). Notably, adjustment for the number of male partners for receptive fellatio did not alter the inverse association with sexual exposure to women (RR = 0.6; 95% CI = 0.4–0.9).

TABLE II – SUBSTANCE USE AND UNIVARIATE ASSOCIATIONS WITH KS

Substance	*n*	KS (%)	RR (95% CI)
Tobacco[1]	331	55 (17)	0.6 (0.5–0.9)
Alcohol[2]	417	88 (21)	1.6 (0.9–3.0)
Nitrate inhalants[3]	382	77 (20)	1.1 (0.7–1.7)
> 50 uses	211	48 (23)	1.3 (0.9–1.9)
Intravenous drugs[3]	96	15 (16)	0.8 (0.5–1.3)
Crack cocaine[2]	66	5 (8)	0.4 (0.1–0.8)
Other cocaine[2]	64	15 (23)	1.2 (0.8–2.0)
Amphetamines[2]	40	4 (10)	0.5 (0.2–1.3)
Heroin[2]	9	1 (11)	0.6 (0.1–3.6)
Painkillers[2]	77	17 (22)	1.1 (0.7–1.8)
Sedatives[2]	70	19 (27)	1.5 (0.9–2.3)
Tranquilizers[2]	67	13 (19)	1.0 (0.6–1.7)

[1]Smoked at least 100 cigarettes in lifetime.
[2]Any use in 12 months prior to enrollment.
[3]Any use in lifetime.

Receipt of money or drugs for sex was inversely associated with KS, and the association persisted in a model that included having paid for sex (received pay RR = 0.6, 95% CI = 0.4–1.0; paid RR = 1.1, 95% CI = 0.7–1.7). In univariate analyses, KS was somewhat less frequent in condom users and enema users and somewhat more frequent in sexual contacts of partners with KS, but these associations were not statistically significant (Table III).

KS was significantly associated with several other AIDS-related illnesses, including those due to cytomegalovirus (RR = 2.0; 95% CI = 1.3–3.2), histoplasmosis (RR = 3.5; 95% CI = 1.9–6.3) and herpes simplex virus type 2 (RR = 1.8; 95% CI = 1.3–2.7; Table IV). KS prevalence was higher in those with a CD4 cell count below 200 cells/mm^3 at enrollment and slightly lower in

TABLE III – SEXUAL BEHAVIORS AND UNIVARIATE ASSOCIATIONS WITH KS

Behavior	*n*	KS (%)	RR (95% CI)
Sexual intercourse with women	371	63 (17)	0.6 (0.4–0.9)
> 5 vaginal partners	99	11 (11)	0.5 (0.3–0.9)
> 5 fellatio partners	80	8 (10)	0.5 (0.2–0.9)
> 5 cunnilingus partners	62	8 (13)	0.6 (0.3–1.2)
Sexual intercourse with men			
> 20 fellatio partners (receptive)	364	77 (21)	1.3 (0.9–2.0)
> 20 fellatio partners (insertive)	348	73 (21)	1.2 (0.8–1.9)
> 20 anal insertive partners	251	46 (18)	0.9 (0.6–1.2)
> 20 anal receptive partners	280	59 (21)	1.2 (0.8–1.7)
Any sex partner with KS	144	33 (23)	1.4 (1.0–2.1)
Ever use of condoms with anal sex	439	81 (18)	0.7 (0.4–1.0)
Ever use of enemas during sex	157	27 (17)	0.8 (0.6–1.2)
> 20 enemas during sex	64	7 (11)	0.5 (0.3–1.1)
Received money or drugs for sex	161	23 (14)	0.6 (0.4–1.0)
Paid money or drugs for sex	127	22 (17)	0.8 (0.6–1.3)

TABLE IV – AIDS-RELATED ILLNESSES AND UNIVARIATE ASSOCIATIONS WITH KS

Illness	*n*	KS (%)	RR (95% CI)
Candidiasis	51	11 (22)	1.1 (0.6–1.9)
Cytomegalovirus disease	35	13 (37)	2.0 (1.3–3.2)
Cryptococcosis	14	4 (29)	1.5 (0.6–3.4)
Cryptosporidiosis	17	3 (18)	0.9 (0.3–2.5)
AIDS dementia	19	4 (21)	1.1 (0.4–2.6)
Histoplasmosis	6	4 (67)	3.5 (1.9–6.3)
Herpes simplex virus type 2	96	30 (31)	1.8 (1.3–2.7)
Mycobacterial avium complex	7	3 (43)	2.2 (0.9–5.3)
Other mycobacterial disease	29	8 (28)	1.4 (0.8–2.7)
Non-Hodgkin's lymphoma	7	1 (14)	0.7 (0.1–4.5)
Pneumocystis carinii pneumonia	104	24 (23)	1.2 (0.8–1.8)
Wasting syndrome	90	23 (26)	1.4 (0.9–2.1)

those with detectable HIV viremia, but neither of these associations was statistically significant (data not shown).

From the univariate analyses, race, income, education, smoking, crack cocaine use, sexual intercourse with women, receipt of money or drugs for sex and history of any non-KS AIDS-related illness were identified as having statistically significant associations with prevalent KS. In a multivariable model including all of these factors, their adjusted associations with KS were qualitatively similar to the univariate RRs. Estimated RRs (95% CI) were 0.6 (0.3–1.1) for black race, 1.0 (0.6–1.6) for annual income over $30,000, 1.3 (0.8–2.1) for completion of college, 0.8 (0.5–1.1) for smoking, 0.5 (0.2–1.3) for crack cocaine use, 0.7 (0.5–1.1) for sexual intercourse with women, 0.8 (0.5–1.2) for pay received for sex and 1.6 (1.0–2.3) for non-KS disease.

Discussion

Previous studies of KS risk in individuals coinfected with HIV and HHV-8 have been primarily limited to laboratory parameters. KS risk has been reported to be higher when HHV-8 seroconversion followed infection with HIV.[11,12] Detection of circulating HHV-8 DNA[18,19] and higher levels of HHV-8 viral load[20] have also been related to KS risk. However, all of these studies were relatively small.

While male homosexual sexual activity is the strongest known risk factor for infection with HHV-8,[21] an association with progression after infection has not been previously shown. In our study, KS was positively associated with sexual activities with men and negatively associated with sexual activities with women and with receiving money or drugs for sex. These associations do not have ready explanations and may be related to unmeasured differences in timing of HIV and/or HHV-8 infection. Alternatively, the associations may reflect superinfection with multiple subtypes of HHV-8 or with other sexually transmitted agents more common among homosexual men.

We identified a number of potential behavioral associations with prior or current KS in this large study of U.S. homosexual men with advanced HIV infection and antibodies against HHV-8. Notably, cigarette smoking was inversely associated with KS. Previous investigations have found similar negative associations between smoking and KS, both classical and AIDS-related. In a study restricted to HHV-8 seropositives, Goedert *et al.*[22] observed that subjects with classical KS were only 25% as likely to be current or former smokers as compared to non-KS controls. In the Multicenter AIDS Cohort Study of HIV-positive male homosexuals, Hoover *et al.*[23] examined KS risk without regard to HHV-8 serostatus and found a 30–39% reduction in smokers. These consistent findings suggest the association is real, warranting further study to elucidate the mechanism. The adverse effects of cigarette smoking likely outweigh any benefit of reducing KS, but the protective constituent(s) of cigarette smoke could potentially be administered with less potential for harm.

Curiously, use of crack cocaine was inversely associated with KS, whereas use of the powder form of the drug was not. If the cocaine association with KS is biologically causal, it potentially varies by route of administration, as crack cocaine is smoked and cocaine powder is usually taken intranasally. However, we did not have information about the amount consumed, and the apparent specificity may conceivably reflect a higher cocaine dose among users of crack. Cocaine use has not been previously associated with KS, and this unexpected finding warrants examination in other populations.

We found positive associations with white race, higher income and advanced education, which may all be markers of higher socioeconomic status. *A priori*, we had expected higher socioeconomic status to be inversely associated with KS, related to better access to effective antiretroviral therapy.[24] Although genetic differences by race may partially account for our findings, it may also

be that better access to medical care results in earlier diagnosis of KS,[25] or that KS is relatively underdiagnosed in individuals with darkly pigmented skin.[26]

We studied homosexual men who were HHV-8 seropositive, and the associations we observed may not apply to other HIV-infected groups. Our study has several noteworthy limitations. The foremost is that the serologic assays used to determine HHV-8 serostatus have imperfect sensitivity and specificity[27] and therefore HHV-8 serostatus may be misclassified. The rate of misclassification may vary among exposure groups that differ by prevalence of male homosexual sexual activity, given the strong association between homosexual behavior and HHV-8. Although the associations of KS with exposures such as sexual activity with women may partly reflect true differences in HHV-8 infection status, sensitivity analysis suggests the overall effect is likely to be minor. For example, if 20% of the bisexual men who did not have KS had been misclassified as HHV-8-positive (*vs*. none of the corresponding unexposed group), adjusting for misclassification of this magnitude would change the RR for sexual intercourse with women from 0.6 to 0.7.

Another limitation of this study is the unknown timing of the various exposures relative to KS diagnosis. It is therefore difficult to infer causality of these associations without determining their temporal sequence. In addition, these cross-sectional associations could be biased by potential differences in relative timing of HHV-8 and HIV infection, a postulated determinant of KS risk.[11]

A third limitation is that the majority of data was collected by interviews without external verification. There could have been problems with recall and participants may have underreported high-risk behavior. However, there is no reason to expect that those with KS would have different reporting patterns than those with other AIDS-defining illnesses; therefore, these potential problems would not be expected to bias the results.

The most intriguing aspect of this analysis is the identification of factors that were inversely associated with progression of HHV-8 infection to KS. Smoking, crack cocaine use, paid sex and having multiple female sexual partners are typically considered risky behaviors in the context of public health. Future research based on this analysis should focus on practical measures for countering KS that do not increase the risk of other diseases.

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Appendix

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